Eyes absent 1 (Eya1) is a critical coordinator of epithelial, mesenchymal and vascular morphogenesis in the mammalian lung.

Journal: Dev Biol

Publication Year: 2011

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PubMed link: 21129374

Funding Grants: CHLA Stem Cell Training Grant

Public Summary:

Scientific Abstract:
The proper level of proliferation and differentiation along the proximodistal axis is crucial for lung organogenesis. Elucidation of the factors that control these processes will therefore provide important insights into embryonic lung development and regeneration. Eya1 is a transcription factor/protein phosphatase that regulates cell lineage specification and proliferation. Yet its functions during lung development are unknown. In this paper we show that Eya1(-/-) lungs are severely hypoplastic with reduced epithelial branching and increased mesenchymal cellularity. Eya1 is expressed at the distal epithelial tips of branching tubules as well as in the surrounding distal mesenchyme. Eya1(-/-) lung epithelial cells show loss of progenitor cell markers with increased expression of differentiation markers and cell cycle exit. In addition, Eya1(-/-) embryos and newborn mice exhibit severe defects in the smooth muscle component of the bronchi and major pulmonary vessels with decreased Fgf10 expression. These defects lead to rupture of the major vessels and hemorrhage into the lungs after birth. Treatment of Eya1(-/-) epithelial explants in culture with recombinant Fgf10 stimulates epithelial branching. Since Shh expression and activity are abnormally increased in Eya1(-/-) lungs, we tested whether genetically lowering Shh activity could rescue the Eya1(-/-) lung phenotype. Indeed, genetic reduction of Shh partially rescues Eya1(-/-) lung defects while restoring Fgf10 expression. This study provides the first evidence that Eya1 regulates Shh signaling in embryonic lung, thus ensuring the proper level of proliferation and differentiation along the proximodistal axis of epithelial, mesenchymal and endothelial cells. These findings uncover novel functions for Eya1 as a critical upstream coordinator of Shh-Fgf10 signaling during embryonic lung development. We conclude, therefore, that Eya1 function is critical for proper coordination of lung epithelial, mesenchymal and vascular development.